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Response Under 37 CFR 1.116
Expedited Procedure
Examining Group 1806

Attorney Docket No.: BD1 CIP FWC IV

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B. Kenn
6/19/97

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Sherie L. Morrison, et al.
Serial No.	:	08/266,154
Filed	:	June 27, 1994
For	:	RECEPTORS BY DNA SPLICING AND EXPRESSION
Art Unit	:	1806
Examiner	:	Julie E. Reeves, Ph.D.

June 11, 1997

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

RESPONSE TO EXAMINER'S ACTION

Sir:

Applicants submit this paper in response to the December 11, 1996 Office Action. Applicants have filed concurrently herewith a petition for a three-month extension of time, together with a check for $930.00 to cover the fee pursuant to 37 C.F.R. § 1.17(c). With the extension, this response is due June 11, 1997.

Applicants respectfully request entry of the following amendments:

To The Specification

Please amend the specification at page 2, lines 25-27 by deleting "(a)", replacing "Figure 1" with "Figure 1A", and replacing "(b)" with "Figure 1B is". The amended text should read:

> "Figure 1A is a schematic diagram of the chimeric mouse:human heavy chain gene vector; and Figure 1B is the chimeric light chain vector."

To The Claims

Please cancel claims 39-41, 45, 47, 54-55, 57-58, 62, 64, 66-69, 73, 75, and 77 without prejudice to renewal.

Kindly amend the pending claims as follows:

K1 46. (Amended) A method as recited in claim 81 [45] wherein the cell is a murine P_3 cell.

K2 48. (Amended) A method as recited in claim 82 [47] wherein the cell is a murine J558L cell.

K3 63. (Amended) A method as recited in claim 87 [62] wherein the cell is a murine P_3 cell.

65. (Amended) A method as recited in claim 88 [64] wherein the cell is a murine J558L cell.

72. (Twice amended) A method as recited in claim 71 [90] wherein the cell is a murine myeloma cell.

74. (Amended) A method as recited in claim 93 [73] wherein the cell is a murine P_3 cell.

76. (Amended) A method as recited in claim 94 [75] wherein the cell is a murine J558L cell.

78. (Amended) A method for producing a functional antibody comprising a heavy chain and a light chain, which comprises the steps of:

(a) transfecting a non-antibody producing mammalian lymphoid cell with a first DNA sequence coding for a first chain of the antibody;

(b) transfecting the cell with a second DNA sequence, said second DNA sequence coding for a second chain of the antibody, said second chain being a chain other than the first chain and said first and second chains being either the heavy chain or the light chain; and

(c) maintaining the cell in a nutrient medium, so that the cell expresses the first and second DNA sequences and the resultant chains are intracellularly assembled together to form the antibody which is then secreted in a form capable of specifically binding to antigen.

82. (Amended) A method as recited in claim 78 wherein the cell endogenously produces an immunoglobulin light chain or an immunoglobulin heavy chain but not both and wherein the heavy chain is not secreted in a form capable of specifically binding to antigen.

83. (Amended) A method as recited in claim 78 wherein the antibody [is a chimeric antibody having] comprises a variable region [substantially the same as that] found in a first mammalian source and [having] comprises a constant region [substantially the same as that] found in a second mammalian source, said second mammalian source being from a mammalian species other than that of the first mammalian source.

84. (Amended) A method for producing a functional antibody comprising a heavy chain and a light chain, which comprises the steps of:

(a) transfecting a non-antibody producing mammalian lymphoid cell with a plasmid comprising a first DNA sequence coding for a first chain of the antibody and a second DNA sequence coding for a second chain of the antibody, said second chain being a chain other than the first chain and said first and second chains being either the heavy chain or the light chain; and

(b) maintaining the cell in a nutrient medium so that the cell expresses said first DNA sequence and said second DNA sequence and the resultant chains are intracellularly assembled together to form the antibody which is then secreted in a form capable of specifically binding to antigen.

88. (Amended) A method as recited in claim 84 wherein the cell endogenously produces an immunoglobulin light chain or an immunoglobulin heavy chain but not both and wherein the heavy chain is not secreted in a form capable of specifically binding to antigen.

89. (Amended) A method as recited in claim 84 wherein the antibody [is a chimeric antibody comprising] comprises a variable region [substantially the same as that] found in a first mammalian source and [comprising] comprises a constant region [substantially the same as that] found in a second mammalian source, said second mammalian source being from a mammalian species other than that of the first mammalian source.

90. (Amended) A method for producing a functional antibody comprising a heavy chain and a light chain which comprises the steps of:

(a) maintaining in a nutrient medium a non-antibody producing mammalian lymphoid cell, said cell having been transfected with a first DNA sequence coding for a first chain of the antibody and a second DNA sequence coding for a second chain of the antibody, said second chain being a chain other than the first chain and said first and second chains being either the heavy chain or the light chain;

(b) expressing from said cell the heavy chain and the light chain functionally assembled together to form said antibody which is then secreted in a form capable of binding antigen; and

(c) recovering said antibody.

94. (Amended) A method as recited in claim 90 wherein the cell endogenously produces an immunoglobulin light chain or an immunoglobulin heavy chain but not both and wherein the heavy chain is not secreted in a form capable of specifically binding to antigen.

95. (Amended) A method as recited in claim 90 wherein the antibody [is a chimeric antibody comprising] comprises a variable region [substantially the same as that] found in a first mammalian source and [having] comprises a constant region [substantially the same as that] found in a second mammalian source, said second mammalian source being from a mammalian species other than that of the first mammalian source.

REMARKS

Applicants note the Examiner's comments concerning the appeal fees and asks that they be refunded and credited to our deposit account no. 06-1075.

Applicants also note with appreciation the withdrawal of the rejection under 35 U.S.C. § 103 and the determination that the claims are free of the prior art.

Specification

Applicants have amended the specification as suggested by the examiner and ask that this objection be withdrawn.

Claim Rejections - 35 U.S.C. § 112

Paragraph 4

Dependent claims 55, 66, 77, and 89 are rejected under 35 U.S.C. § 112. Claims 55, 66, and 77 have been canceled. In the December 4, 1996 interview and in the December 11, 1996 office action, the examiner suggested that these claims be amended by deleting "chimeric". The examiner first asserts that use of the word "chimeric" renders the claim indefinite. While applicants believe that this term is adequately defined in the specification (p. 2, line 37 - p. 3, line 15), applicants have amended claims 83, 89 and 95*

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* The Examiner did not reject claims 83 and 95 on this ground. However, because these claims also contain the word "chimeric," applicants have amended them.

in recognition of the diverse usage of the term "chimeric" by those of skill in the art. However, applicants do not intend any narrowing of the claims by this amendment.

The examiner also asserts that the claims containing the word "chimeric" are not enabled. This ground of rejection is obviated by applicants' amendment in response to the foregoing indefiniteness rejection. However, applicants believe that the claims were fully enabled prior to amendment. Applicants note that this is a pioneering invention in the field of recombinant antibodies and is thus entitled to broad claims that may cover later improvements, including those that may have been made during the pendency of this application. Applicants have been urging the Patent Office to issue this application while years of development in this field have been ongoing and submit that it is not appropriate to cite that development as a basis for rejection of these claims.

The examiner also suggested that applicants remove the term "substantially the same as" from these claims on the grounds that it is not clear what changes leave the antibody region "substantially the same as" that found in the mammalian source. Applicants have deleted this language. Again, applicants do not intend to narrow the claims by this amendment. Further, applicants believe that the specification makes clear what variations from the mammalian source are contemplated. See, e.g.:

> "In some instances it will be necessary to provide adapters to join the intron or truncated intron to the constant region." (p. 6, lines 25-29.)

However, because applicants believe that such variations are still within the scope of the amended claims and because applicants are anxious to have these claims allowed, the amendment proposed by the examiner has been made.

Similarly, applicants believe that the contemplated variations are enabled. Those of skill in the art would have known how to add adaptors, leader sequences, etc. to the mammalian antibody region. However, the deletion of "substantially the same as" moots the examiner's enablement rejection on this ground also.

Paragraph 5

Claims 47, 64, 75, and 94 are also rejected under 35 U.S.C. § 112. Claims 47, 64, and 75 have been canceled. Claims 82, 88 and 94* have been amended to remove this rejection.

These claims recite that the non-antibody producing cell "endogenously produces an immunoglobulin light chain or an immunoglobulin heavy chain but not both." The examiner states that it is not clear how a cell line expressing a heavy chain can be considered a non-antibody producing cell as the heavy chain alone can bind antigen. However, applicants disagree that this makes the cell antibody-producing. A heavy chain alone is usually not secreted and is therefore not "produced" by the cell as is an assembled heavy chain-light chain dimer. Even if it is secreted, applicants have amended the claims

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* As with the previous rejection, claims 82 and 88 were not rejected. However, because they contain the same language as the rejected claims, applicants have amended them.

to eliminate this concern. Specifically, applicants have added the limitation "wherein the heavy chain is not secreted in a form capable of specifically binding to antigen."

Paragraph 6

The examiner has rejected claims 39-41, 43-48, 54-55, 57-58, 60-69, and 71-95 for failing to provide an enabling disclosure because they recite *mammalian* host cells. Claims 39-41, 45, 47, 54-55, 57-58, 62, 64, 66-69, 73, 75, and 77 have been canceled. The recitation of mammalian cells is consistent with the specification which reads:

> "Introduction of the fused genes into an appropriate *eukaryotic host cell* under conditions for expression and processing provides for a functional assembled multi-subunit receptor product." (p. 2, lines 18-22; emphasis added.)
>
> "In order for expression of the fused gene, it will be necessary to have transcriptional and translational signals recognized by an appropriate eukaryotic host. For the most part, desirable eukaryotic hosts will be mammalian cells capable of culture in vitro, particularly leukocytes, more particularly myeloma cells, or other transformed or oncogenic lymphocyte, e.g., EBV transformed cells. Alternatively, non-mammalian cells may be employed, such as fungi, e.g., yeast, filamentous fungi, or the like." (p. 8, lines 29-38.)

While this disclosure in the specification provides support for claiming antibody expression in any mammalian (and even non-mammalian) cells, the examiner asserts that "the field of expressing immunoglobulin genes into non-lymphoid mammalian cells was unpredictable at the time the application was filed."

During the December 4, 1996 telephone interview (Paper 49), the Examiner advised that claims reciting "mammalian lymphoid" host cells are allowable. Accordingly, the Examiner rejected the above-cited claims because they include transfection of mammalian "cells which do not normally produce antibody light and heavy chains."

Applicants believe that by amending the claims to recite "mammalian lymphoid" host cells they have achieved the Examiner's objective of not including host cells which do not normally produce antibody light and heavy chains. While there is no genetic marker to determine whether a cell is lymphoid, lymphoid cells have been described as "cells of the immune system" that are "organized into lymphoid organs." (Roitt et al., (1989) Immunology, 2d ed., p. 1.1. London: Gower Medical Publishing.) An immunology text contemporaneous with the filing of this application states, "[t]he introduction of an immunogen into a responsive individual leads to extensive changes in the responding tissue. This response usually takes place in organs containing large numbers of the involved cells, i.e., lymphocytes, macrophages, and plasma cells. These cells are known as lymphoid cells...." (Sell, Stewart. (1975) Immunology, Immunopathology, and Immunity, ch. 3, Harper & Row, Hagerstown, Maryland.) According to Roitt, "[t]he immune reaction can take the form of cell-mediated immunity or may involve the production of antibodies directed towards the antigen...." (p. 8.1.) The sum of the foregoing is that lymphoid cells include cells that produce antibodies and

antibody-producing cells are lymphoid in origin. Given that, applicants' amendment of the claims to recite "mammalian lymphoid" host cells cures any alleged lack of enablement.

A declaration has come to applicants' attention that was submitted in a foreign patent proceeding in opposition to the foreign counterpart of the Cabilly patent that has been cited during the prosecution of this application. As set forth in the Declaration of Sherie L. Morrison submitted herewith, none of the exhibits that are attached to that declaration is enabling of applicants' invention. Moreover, Applicants do not believe that the exhibits to that declaration constitute prior art* to applicants' invention, with one possible exception. Exhibit D to the May 15, 1996 Declaration of Marc J. Shulman may have been published prior to the October 19, 1983 date that applicants swore behind in previously submitted declarations pursuant to 37 C.F.R. § 131. However, it, like the other exhibits, is not enabling.

In view of the foregoing, applicants believe that the pending claims are in condition for allowance. Accordingly, entry of the present amendment and allowance of the claims are requested.

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* For example, Exhibit D to the 1994 Declaration (attached to the 1996 declaration) constitutes slides shown during a lecture. Those slides are not prior art. Regents of the University of California v. Howmedica, Inc., 210 USPQ 727, 738 (D.N.J. 1981). Nothing in the declaration suggests that copies of those slides were distributed.

If the Examiner has any questions or reservations about the allowability of these claims, applicants request that the Examiner telephone the undersigned attorney at (415) 617-4011.

Respectfully submitted,

Vicki S. Veenker

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I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231,
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Vicki S. Veenker
Name of Person Signing Certificate

Vicki S. Veenker
Signature of Person Signing Certificate

June 11, 1997
Date of Signature

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Response Under 37 CFR 1.116
Expedited Procedure
Examining Group 1806

REV. 4/97
For Other Than A Small Entity

Docket No. BD1 CIP FWC IV

Applicant(s)	:	Sherie L. Morrison, et al.
Serial No.	:	08/266,154
Filed	:	June 27, 1994
For	:	RECEPTORS BY DNA SPLICING AND EXPRESSION
Group Art Unit	:	1806
Examiner	:	Julie E. Reeves, Ph.D.

18X

Hon. Assistant Commissioner
for Patents
Washington, D.C. 20231

Palo Alto, California
June 11, 1997

TRANSMITTAL LETTER

Sir:

Transmitted herewith: [ ] a Preliminary Amendment; [X] a Response to Examiner's Action; [ ] a Supplemental Amendment; [ ] a substitute Specification; [X] a Declaration; [ ] a Supplemental Declaration; [ ] a Power of Attorney; [ ] an Associate Power of Attorney; [ ] formal drawings; to be filed in the above-identified patent application.

FEE FOR ADDITIONAL CLAIMS

[X] A fee for additional claims is not required.

[ ] A fee for additional claims is required.

The additional fee has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA	RATE	ADDITIONAL FEES
TOTAL CLAIMS	30	-	48	* =	0	X $22 =	$0
INDEPENDENT CLAIMS	3	-	6	** =	0	X $80 =	$0
FIRST PRESENTATION OF A MULTIPLE DEPENDENT CLAIM						+ $260 =	$0
						TOTAL	$0

* If less than 20, insert 20.

** If less than 3, insert 3.

[ ] A check in the amount of $_____ in payment of the filing fee is transmitted herewith.

[X] The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 C.F.R. § 1.16, in connection with the paper(s) transmitted herewith, or credit any overpayment of same, to deposit Account No. 06-1075. A duplicate copy of this transmittal letter is transmitted herewith.

[ ] Please charge $_____ to Deposit Account No. 06-1075 in payment of the filing fee. A duplicate copy of this transmittal letter is transmitted herewith.

EXTENSION FEE

[X] The following extension is applicable to the Response filed herewith; [ ] $110.00 extension fee for response within first month pursuant to 37 C.F.R. § 1.17(a); [ ] $390.00 extension fee for response within second month pursuant to 37 C.F.R. § 1.17(b); [X] $930.00 extension fee for response within third month pursuant to 37 C.F.R. § 1.17(c); [ ] $1,470.00 extension fee for response within fourth month pursuant to 37 C.F.R. § 1.17(d).

[X] A check in the amount of [ ] $110.00; [ ] $390.00; [X] $930.00; [ ] $1,470.00; in payment of the extension fee is transmitted herewith.

[X] The Commissioner is hereby authorized to charge payment of any additional fees required under 37 C.F.R. § 1.17 in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 06-1075. A duplicate copy of this transmittal letter is transmitted herewith.

[ ] Please charge the [ ] $110.00; [ ] $390.00; [ ] $930.00; [ ] $1,470.00; extension fee to Deposit Account No. 06-1075. A duplicate copy of this transmittal letter is transmitted herewith.

Vicki S. Veenker

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I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231,

on June 11, 1997

Vicki S. Veenker
Name of Person Signing Certificate

Vicki S. Veenker
Signature of Person Signing Certificate

June 11, 1997
Date of Signature